



PCT/EP 03/08085

10/521297

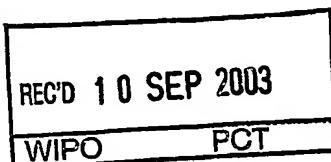
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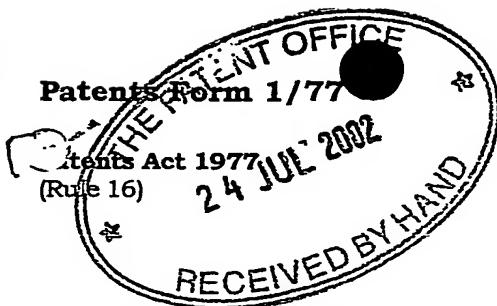
Signed

Dated

R. Mahoney

16 June 2003

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PCT/EP 03 / 08085

1/77
JUL02 E735783-5 D005
1/7700 0.00-0217152.6

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

24 JUL 2002

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1. Your reference	4-32510P1		
2. Patent application number <i>(The Patent Office will fill in this part)</i>	0217152.8		
3. Full name, address and postcode of the or of each applicant <i>(underline all surnames)</i>	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND <i>7125487005</i>		
Patent ADP number <i>(if you know it)</i> If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND		
4. Title of invention	Organic compounds		
5. Name of your agent <i>(if you have one)</i> "Address for service" in the United Kingdom to which all correspondence should be sent <i>(including the postcode)</i>	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		
Patents ADP number <i>(if you know it)</i>	1800001		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and <i>(if you know it)</i> the or each application number	Country	Priority application number <i>(if you know it)</i>	Date of filing (day/month/year))
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day/month/year)
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? <i>(Answer 'Yes' if:</i>	Yes		
<i>a) any applicant named in part 3 is not an inventor, or</i>			
<i>b) there is an inventor who is not named as an applicant, or</i>			
<i>c) any named applicant is a corporate body.</i>			
<i>(see note (d))</i>			

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description	4
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

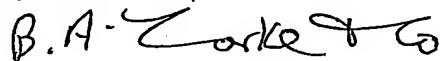
Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application

Signature

Date



B.A. Yorke & Co.

24 July 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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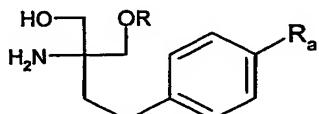
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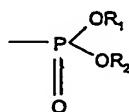
Organic Compounds

The present invention relates to a new use for 2-amino-2-propane-1,3-diols in free form or in pharmaceutically acceptable salt form.

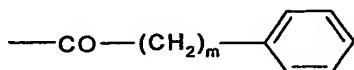
The compounds for use according to the invention are compounds of formula I



wherein R is H or a residue of formula (a)



wherein each of R₁ and R₂ is H or C₁₋₄alkyl optionally substituted by halogen atoms, and R_a is octyl or



wherein m is 2 to 9, or a pharmaceutically acceptable salt thereof.

Compounds of formula I are disclosed e.g. in U.S. Patent Nos. 5,604229, EP-A1-1,002,792 and in WO 02/18395A, incorporated herein by reference in their entirety. Preferred compounds are 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, in free form or in pharmaceutically acceptable salt form (hereinafter FTY720), e.g. the hydrochloride salt, and its phosphate (R is a residue of formula (a)) and 2-amino-2-[2-[4-(1-oxo-5-phenylpentyl)phenyl]ethyl]propane-1,3-diol ("Compound Y") in free form or in a pharmaceutically acceptable salt form.

When R is a residue of formula (a) the compounds of formula I have one asymmetric center in the molecule and the present invention is to be understood as embracing the optical isomers as well as racemates and mixtures thereof.

Examples of the pharmaceutically acceptable salts of the compounds of formula I include salts with inorganic acids, such as hydrochloride, hydrobromide and sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate and benzenesulfonate salts, and when R is a residue of formula (a), salts

with metals such as sodium, potassium, calcium and aluminium, salts with amines, such as triethylamine and salts with dibasic amino acids, such as lysine. Compounds of formula I and salts of the present invention encompass hydrate and solvate forms.

Compounds of formula I have, on the basis of observed activity, e.g. as described in EP-A1-627,406 or EP-A1-1,002,792 been found to be useful e.g. as immunosuppressants, e.g. in the treatment of acute allograft rejection or autoimmune disorders. In accordance with the present invention, it has now surprisingly been found that the compounds of formula I have a beneficial effect on chronic heart failure.

Chronic heart failure is a clinical syndrome characterized by distinctive symptoms and signs resulting from disturbances in cardiac output, e.g. inadequate for the body's needs. It is often associated with other changes such as cardiac hypertrophy and myocardial ischemia.

In accordance with the particular findings of the present invention, there is provided:

- 1.1 A method for treating chronic heart failure in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
- 1.2 A method for improving heart energy efficiency and/or reducing its oxygen needs in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
- 1.3 A method for improving cardiac output in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
- 1.4 A method for treating arrhythmia or tachyarrhythmia, e.g. atrial fibrillation, atrial flutter or sinus ventricular tachycardia, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

2. A compound of formula I or a pharmaceutically acceptable salt thereof, for use in a method as defined under 1.1 to 1.4 above; or
3. A compound of formula I or a pharmaceutically acceptable salt thereof, for use in the preparation of a pharmaceutical composition for use in a method as defined under 1.1 to 1.4 above; or

4. A pharmaceutical composition for use in a method as defined under 1.1 to 1.4 above comprising a compound of formula I or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor.

Utility of the compounds of formula I in free form or in pharmaceutically acceptable salt form, e.g. in the treatment of chronic heart failure, as hereinabove specified, may be demonstrated in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

A. *In vivo*

The effect of a compound of formula I on chronic heart failure is tested in rabbits where heart failure is induced as a consequence of a large myocardial infarction (RP. Hof et al. J. Cardiovasc. Pharmacol., 1991, 18,361-368). The changes of atrial natriuretic factor are a reliable indicator of the status of the heart failure in this animal model. When administered i.v. at a dose of from 0.1 to 10 mg/kg, the compounds of formula I, e.g. 2-amino-2-[2-(4-octylphenyl) ethyl]propane-1,3-diol, hydrochloride, have a beneficial effect on the heart failure.

Daily dosages required in practicing the method of the present invention will vary depending upon, for example, the compound used, the host, the mode of administration, the severity of the condition to be treated. A preferred daily dosage range is about from 0.03 to 2.5 mg/kg per day as a single dose or in divided doses. Suitable daily dosages for patients are on the order of from e.g. 0.5 to 50 mg p.o. Suitable unit dosage forms for oral administration comprise from ca. 0.1 to 25 mg active ingredient, e.g. FTY720 or Compound Y, e.g. in hydrochloride form, together with one or more pharmaceutically acceptable diluents or carriers therefor. As an alternative, the compound of formula I may also be administered twice or three times a week, e.g. at a dosage as indicated above.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Pharmaceutical compositions comprising a compound of formula I may be manufactured in conventional manner, e.g. as described in EP-A1-627,406 or in EP-A1-1,002,792.

The compounds of formula I may be administered as the sole ingredient or together with other drugs, e.g. an angiotensin converting enzyme inhibitor, e.g. Benazepril, an angiotensin II receptor blocker, e.g. Valsartan, Losartan, Irbesartan, Eprosartan,

Candesartan, Tasosartan or Telemisartan, other drugs used in patients with heart failure, e.g. digoxin or digitalis preparations, a β -blocker, a β -adrenergic receptor agonist, e.g. salbutamol, an α -2 receptor agonist, a calcium antagonist, or a diuretic, e.g. hydrochlorothiazide or spironolactone.

Where the compounds of formula I are administered in conjunction with other drugs, dosages of the co-administered compound will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition to be treated, and so forth. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

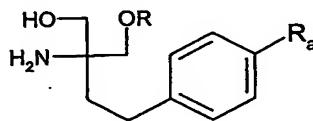
In accordance with the foregoing the present invention provides in a yet further aspect:

5. A pharmaceutical combination comprising a) a first agent which is a compound of formula I, e.g. FTY720 or Compound Y, or a pharmaceutically acceptable salt thereof, and b) a co-agent, e.g. a second drug agent as defined above.
6. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of formula I, e.g. FTY720 or Compound Y, or a pharmaceutically acceptable salt thereof, and a second drug substance, e.g. as indicated above.

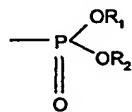
Compounds of formula I in free form or in pharmaceutically acceptable salt form are well tolerated at dosages required for use in accordance with the present invention. For example, the acute LD₅₀ is > 10 mg/kg p.o. in rats and monkeys for FTY720.

Claims

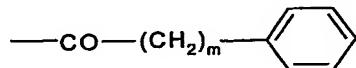
1. A method for treating chronic heart failure in a subject in need thereof comprising administering to said recipient a therapeutically effective amount of a compound of formula I



wherein R is H or a residue of formula (a)



wherein each of R₁ and R₂ is H or C₁₋₄alkyl optionally substituted by halogen atoms, and R_a is octyl or



wherein m is 2 to 9, or a pharmaceutically acceptable salt thereof.

2. A method for improving heart energy efficiency and/or reducing its oxygen needs in a subject in need thereof comprising administering to said recipient a therapeutically effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof;
3. A method for improving cardiac output in a subject in need thereof comprising administering to said recipient a therapeutically effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof.
4. A method for treating arrhythmia or tachyarrhythmia in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.
5. A compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof, for use in a method according to any one of claims 1 to 4.
6. A compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof, for use in the preparation of a pharmaceutical composition for use in a method according to any one of claims 1 to 4.

7. A pharmaceutical composition for use in a method according to any one of claims 1 to 4 above comprising a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor.
8. A pharmaceutical combination comprising a) a first agent which is a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof and b) a co-agent selected from an angiotensin converting enzyme inhibitor, an angiotensin II receptor blocker, an α -2 receptor agonist, a calcium antagonist, a β -blocker, a β -adrenergic receptor agonist or a diuretic.
9. A method according to any one of claims 1 to 4 comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof, and a second drug substance.